

APPLICANTS: Dobie *et al.*
SERIAL NO: 10/714,796

DOCKET NO: HTS-0016US.P1 (ISIS.037CP1)

AMENDMENTS TO THE SPECIFICATION:

Please replace paragraph [0054] with the following:

[0054] Such double stranded oligonucleotide moieties have been shown in the art to modulate target expression and regulate translation as well as RNA ~~processsing~~ processing via an antisense mechanism. Moreover, the double-stranded moieties may be subject to chemical modifications (Fire *et al.*, *Nature*, 1998, 391, 806-811; Timmons and Fire, *Nature* 1998, 395, 854; Timmons *et al.*, *Gene*, 2001, 263, 103-112; Tabara *et al.*, *Science*, 1998, 282, 430-431; Montgomery *et al.*, *Proc. Natl. Acad. Sci. USA*, 1998, 95, 15502-15507; Tuschl *et al.*, *Genes Dev.*, 1999, 13, 3191-3197; Elbashir *et al.*, *Nature*, 2001, 411, 494-498; Elbashir *et al.*, *Genes Dev.* 2001, 15, 188-200). For example, such double-stranded moieties have been shown to inhibit the target by the classical hybridization of antisense strand of the duplex to the target, thereby triggering enzymatic degradation of the target (Tijsterman *et al.*, *Science*, 2002, 295, 694-697).

Please replace paragraph [0149] with the following:

[0149] The mouse brain endothelial cell line b.END was obtained from Dr. Werner Risau at the Max Plank ~~Institute~~ Institute (Bad Nauheim, Germany). b.END cells were routinely cultured in DMEM supplemented with 10% fetal bovine serum (Gibco/Life Technologies, Gaithersburg, MD). Cells were routinely passaged by trypsinization and dilution when they reached 90% confluence. Cells were seeded into 24-well plates (Falcon-Primaria #3047) at a density of 40,000 cells/well for use in RT-PCR analysis.

Please replace paragraph [0169] with the following:

[0169] In accordance with the present invention, a series of oligonucleotides were designed to target different regions of the human kinesin-like 1 RNA, using published sequences (GenBank accession number NM_004523.1, incorporated herein as SEQ ID NO: 3). The oligonucleotides are shown in Table 1. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 1 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-methoxyethyl 2'-

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methoxyethoxy (2'-MOE) nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human kinesin-like 1 mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments in which T-24 cells were treated with the antisense oligonucleotides of the present invention. If present, "N.D." indicates "no data".

Please replace paragraph [0196] with the following:

[0196] In accordance with the present invention, a series of oligonucleotides were designed to target different regions of the human kinesin-like 1 RNA, using published sequences (GenBank accession number NM_004523.1, incorporated herein as SEQ ID NO: 3; GenBank accession number NT_030059, incorporated herein as SEQ ID NO: 76; GenBank accession number NM_004523.2, incorporated herein as SEQ ID NO: 77; GenBank accession number BL050421.1, incorporated herein as SEQ ID NO: 78; and GenBank accession number BX103943.1, incorporated herein as SEQ ID NO: 79). The oligonucleotides are shown in Table 16. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 16 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of 2'-~~methoxyethyl~~ 2'-methoxyethoxy (2'-MOE) nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on human kinesin-like 1 mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments in which T-24 cells were treated with the antisense oligonucleotides of the present invention. As noted, some of the compounds were designed to be fully complementary to more than one animal species (human, mouse, and/or rat).

Please replace paragraph [0197] with the following:

[0197] A series of oligonucleotides were designed to target different regions of the mouse

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kinesin-like 1 RNA, using published sequences (GenBank accession number AJ223293.1, incorporated herein as SEQ ID NO: 155; and GenBank accession number BB658933.1, incorporated herein as SEQ ID NO: 156). The oligonucleotides are shown in Table 17. "Target site" indicates the first (5'-most) nucleotide number on the particular target sequence to which the oligonucleotide binds. All compounds in Table 17 are chimeric oligonucleotides ("gapmers") 20 nucleotides in length, composed of a central "gap" region consisting of ten 2'-deoxynucleotides, which is flanked on both sides (5' and 3' directions) by five-nucleotide "wings". The wings are composed of ~~2'-methoxyethyl~~ 2'-methoxyethoxy (2'-MOE) nucleotides. The internucleoside (backbone) linkages are phosphorothioate (P=S) throughout the oligonucleotide. All cytidine residues are 5-methylcytidines. The compounds were analyzed for their effect on mouse kinesin-like 1 mRNA levels by quantitative real-time PCR as described in other examples herein. Data are averages from two experiments in which b.END cells were treated with the antisense oligonucleotides of the present invention. As noted, some of the compounds were designed to be fully complementary to more than one animal species (human, mouse, and/or rat).